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J. N. A. Clegg-Lamptey, FRCSEd, Consultant Surgeon, C. Amenuveve, FWACS, Consutant Surgeon and W. M. Hodasi, FWACS, Consutant Surgeon, Department of Surgery, Korle Bu Teaching Hospital Accra, Ghana

Request for reprints to: Dr. J. N. A. Clegg-Lamptey, Department of Surgery, Korle Bu Teaching Hospital, Accra, Ghana

HEREDITARY NON-POLYPOSIS COLORECTAL CARCINOMA (HNPCC) IN A GHANAIAN FAMILY

J. N. A. CLEGG-LAMPTEY, C. AMENUVEVE and W. M. HODASI

SUMMARY

Colorectal cancer (CRC) is relatively uncommon in Sub Saharan Africa because of relative young age of the population, rarity of pre-malignant conditions and favourable dietary factors. The role of heredity in its causation in Africa is, however, unknown. Four first degree relatives were treated for CRC within three years by the same surgical team in Accra. Two presented with colo-colic intussusception, and the other two with partially obstructing hepatic flexure tumours. Family history revealed that six of eight siblings had developed colorectal cancer, with incidence in three consecutive generations. This family satisfied Amsterdam criteria (I and II) for Lynch syndrome: three generations affected, six of them below age 50, with proximal colon tumours. Genetic testing showed loss of mismatched repair protein gene MSL2.

INTRODUCTION

Colorectal carcinoma (CRC) is the third leading malignancy globally and the fourth leading cause of cancer deaths (1). However, in Africa colorectal carcinoma is not as common as in the Western World.

The relative rarity of CRC in Africa has been attributed to the relatively young age of the population (2), relative absence of precancerous conditions and more favourable 'environmental factors' that cause CRC.

Another cause of CRC is genetic predisposition, typified by Familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC). A strong family history and findings at colonoscopy may heighten suspicion, but they can only be confirmed through gene testing. Cancers arising from genetic predisposition tend to occur at an early age and run in families.

Although the incidence of CRC from HNPCC in Sub Saharan Africa (SSA) is generally unreported, there are published and anaecdotal reports of CRC in many patients occurring below age 30 years. However, many in SSA do not know their family medical histories. It is thus not usual to elicit histories that suggest hereditary CRC.

It is also very unusual to have many patients from the same family reporting with colonic carcinoma to the same medical or surgical team within a short period of time, as the cases we now report.

CASE REPORTS

We treated four members of one family with carcinoma of the large bowel during a three-year period (2003-2006) Table 1.

Table 1
Summary of Sibling A

Case 1 (Event 4. J, Daughter of Sibling A)	
Sex:	Female
Age:	26
Date:	10 April 2003
Diagnosis:	Carcinoma of the colon (Presenting as intussusception)
Site:	Caecum
Operation:	Right hemicolectomy
Histology:	Mucinous carcinoma of Caecum Dukes C
Case 2 (Event 5. Sibling A)	
Sex	Female
Date:	May 2003
Age:	50
Diagnosis:	Colo-colic intussusception from colonic tumour
Site:	Ascending colon
Operation:	Right hemicolectomy
Histology:	Adenocarcinoma, Mucinous. Dukes C

Date:	February 2004
Age:	51
Diagnosis	Carcinoma of colon
Site:	Descending colon
Operation	Left hemicolectomy
Histology:	3 Ulcerated lesions (Moderately-differentiated adenocarcinoma, Dukes C)

Case 3 (Event 6. Sibling B)

Sex:	Male
Date:	December 2005
Age:	49
Diagnosis	Carcinoma of colon
Site:	Hepatic flexure.
Operation	Right hemicolectomy
Histology:	Invasive mucin-secreting adenocarcinoma (Dukes C) at hepatic flexure. Villous adenoma present in the caecum.

Case 4 (Event 7; Sibling E)

Sex:	Female
Date:	December 2006
Age:	44
Diagnosis	Carcinoma of colon
Site:	Hepatic flexure
Operation	Right hemicolectomy
Histology:	Dukes C adenocarcinoma. Mucinous

The first two patients, J and her mother (Sibling A) were seen within a period of one month by our surgical team, both of them presenting with colo-colic intussusceptions from right-sided colonic tumours. Sibling A had had a villous adenomatous polyp removed from her sigmoid colon four years earlier. Unfortunately she did not submit to surveillance colonoscopy until she was admitted with ascending colon carcinoma and later with left colon cancer.

Later, Sibling B and E presented over a period of one year with bloody stools and colicky right-sided abdominal pain from partially obstructing tumours in the hepatic flexure.

Sibling E then revealed a very strong history of colonic cancers that the others had attributing it to evil forces. Three previous siblings, apart from the ones we had treated, had had colonic cancer. Her mother and aunt, both deceased, had also suffered from the disease. No medical history was available from previous generations.

Construction of the family tree showed a very striking picture of colonic cancers in three generations (Figure 1). Only the two youngest (twins) out of 8 siblings in the second generation had been spared from colon cancer. The ages of the siblings at diagnosis is shown in Table 2.

Paraffin tissue blocks from the four patients, analysed at Mayo Clinic, for the four DNA mismatch repair genes showed that all the siblings showed evidence of germline MSH2 mutation, confirming Lynch syndrome.

Figure 1

Family tree showing siblings (and a daughter) and order of colonic cancer events

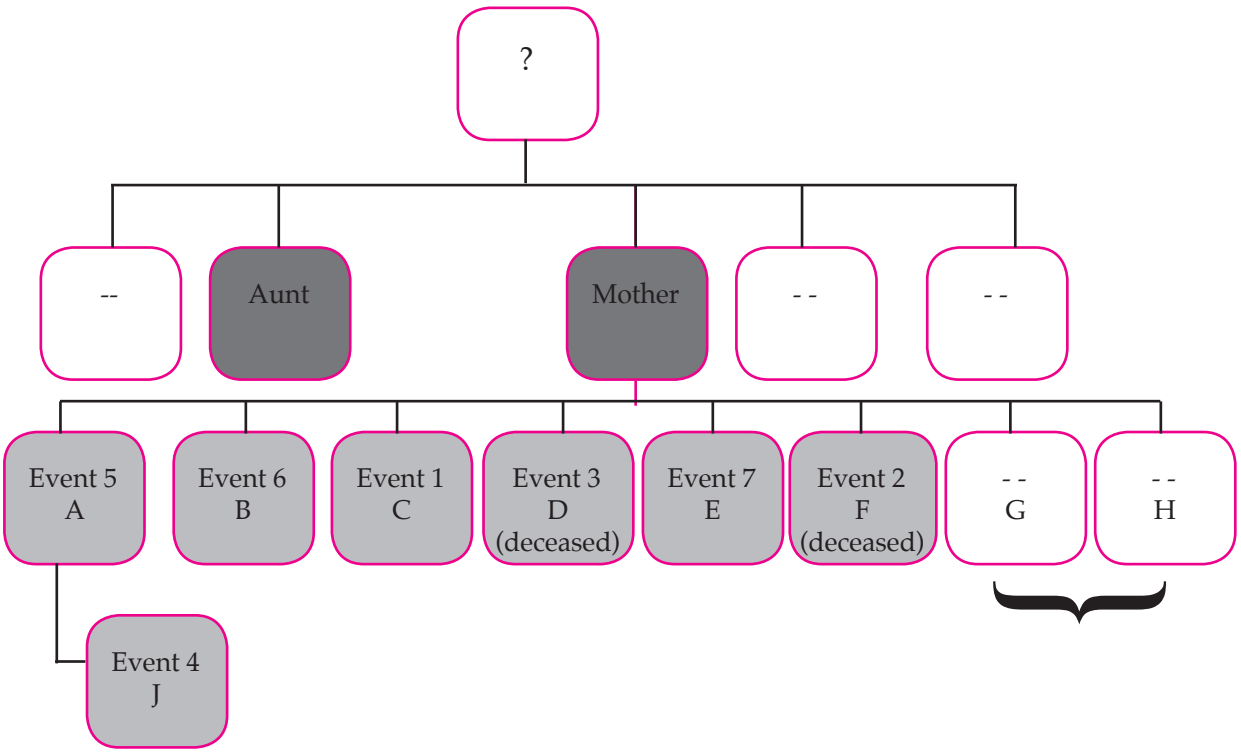

Table 2
Sex and age at diagnosis of Siblings and daughter

Patient	Sex	Age	
C	Male	30	Alive
F	Female	28	Deceased
D	Male	36	Deceased
J	Female	26	Alive
A	Female	50	Alive
B	Male	49	Alive
E	Female	44	Alive

DISCUSSION

In this series of cases of classical Lynch syndrome, CRC occurred in three generations of the family, four of them occurred below the age of 40, and were predominantly proximal colon, mucinous tumours, with one synchronous/metachronous occurence.
A similar report of HNPCC occurring in 16 males over three generations has been reported from South Africa (3).

Hereditary non-polyposis colorectal cancer (HNPCC) is the most frequent cause of hereditary colorectal cancer and results from germline mutations in DNA mismatch repair (MMR) genes, principally MSH2, MLH1, MSH6 and PMS2 (4).

HNPCC is defined both clinically by the Amsterdam criteria (Table 3) and genetically. Like our patients, those who fulfil the original Amsterdam criteria and have hereditary DNA mismatch repair (MMR) gene mutation have Lynch syndrome (5).

The role of HNPCC in the aetiology of colorectal cancer in Sub-Saharan Africa is not clear. In a random study of five colorectal cancer patients in Nigeria, Adebamowo et al reported mutation of MSH2 in two of them (6). However, in a review of CRC in Ain Shams Egypt, none of 177 patients fulfilled the Amsterdam criteria, although 38% of them were below the age of 40 (7). In another study comparing CRC in black and white South Africans, the blacks were younger (41% <50 years) compared with whites (10% <50 years) and loss of MMR protein expression was more evident in blacks (8).

Could many of the young people below the age of 40 (or even 30) in SSA have HNPCC? The question remains unanswered, because unfortunately poor record keeping, inadequate histories and inability perform gene testing have made identification of hereditary CRC largely undocumented.

This series illustrates the problems of managing CRC patients in SSA. One is the unwillingness to submit to follow-up surveillance. Indeed, none of the family members in this report have been reporting since reported for colonoscopy. Lynch has suggested that patients who are noncompliant with colonoscopy, and are MMR mutation positive, may be candidates for prophylactic colectomy (9).

The problem of late presentation of cancers is also illustrated: all four had Dukes C cancer. Indeed, up to 58% CRC in Ghana are stage C1 and C2 (10).

Table 3
Original and revised Amsterdam criteria (4)

Original (Amsterdam I)	Revised (Amsterdam II)
At least 3 relatives with colorectal cancer, one of whom must be a first degree	At least 3 relatives with HNPCC-associated cancer.
relative of the other two.	One should be 1st degree relative of other two.
Involvement of 2 or more generations.	At least 2 successive generations affected.
At least 1 diagnosed before age 50.	At least 1 case diagnosed before age 50.
Familial adenomatous polyposis excluded.	Familial adenomatous polyposis has been excluded.
	Tumours should be verified by pathologic examination.

In conclusion, the incidence of hereditary colorectal cancer in SSA may be more than is generally thought. This series of cases of Lynch syndrome in a family where three generations have been affected illustrates some of the problems of management of CRC in SSA.

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